Antibiotic dose optimisation in the critically ill: targets, evidence and future strategies

Christopher J. Dyer[a,b,c], *Jan J. De Waele*[d,e] *and Jason A. Roberts*[a,b,c,f]

Purpose of review
To highlight the recent evidence for antibiotic pharmacokinetics and pharmacodynamics (PK/PD) in enhancing patient outcomes in sepsis and septic shock. We also summarise the limitations of available data and describe future directions for research to support translation of antibiotic dose optimisation to the clinical setting.

Recent findings
Sepsis and septic shock are associated with poor outcomes and require antibiotic dose optimisation, mostly due to significantly altered pharmacokinetics. Many studies, including some randomised controlled trials have been conducted to measure the clinical outcome effects of antibiotic dose optimisation interventions including use of therapeutic drug monitoring. Current data support antibiotic dose optimisation for the critically ill. Further investigation is required to evolve more timely and robust precision antibiotic dose optimisation approaches, and to clearly quantify whether any clinical and health-economic benefits support expanded use of this treatment intervention.

Summary
Antibiotic dose optimisation appears to improve outcomes in critically ill patients with sepsis and septic shock, however further research is required to quantify the level of benefit and develop a stronger knowledge of the role of new technologies to facilitate optimised dosing.

Keywords
antibiotic, critically ill, outcomes, pharmacodynamic, pharmacokinetic

INTRODUCTION

Sepsis and septic shock are an ongoing cause of high morbidity and mortality in critically ill patients underscoring the need for prompt and precise therapeutic intervention, especially with regards to antibiotic therapy [1–3]. Current evidence shows delayed initiation or inappropriate antibiotic therapy is associated with substantially poorer outcomes, including increased mortality rates [4], emphasising an ongoing need for improved antibiotic dosing in these patients. The study of antibiotic pharmacokinetic and pharmacodynamic (PK/PD) dose optimisation, including the use of therapeutic drug monitoring (TDM) has aimed to address this need by improving the accuracy of therapy, with mounting evidence supporting improving clinical outcomes [5]. This brief review will (i) outline PK/PD principles in relation to antibiotic use, (ii) emphasise the rationale for dose optimisation in the critically ill, (iii) assess the current evidence surrounding TDM and precision dosing strategies as well as review target antibiotic concentrations. Further we aim to (iv) summarise the limitations of current approaches to antibiotic dose optimisation and research and (v) describe future methods in technology and research to improve dose optimisation approaches and outcomes for critically ill patients.

[a]Herston Institute of Infectious Diseases (HeIDI), Metro North Health, [b]Pharmacy Department, [c]Departments of Pharmacy and Intensive Care Medicine, Royal Brisbane and Women's Hospital (RBWH), Herston, Australia, [d]Department of Critical Care Medicine, Ghent University Hospital, [e]Dept of Internal Medicine and Pediatrics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium and [f]UQ Centre for Clinical Research (UQCCR), Faculty of Medicine, University of Queensland, Herston, Australia

Correspondence to Professor Jason A. Roberts, University of Queensland Centre for Clinical Research, The University of Queensland, Brisbane, Qld 4072, Australia. Tel: +61 7 3346 6074;
e-mail: j.roberts2@uq.edu.au

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KEY POINTS

- Antibiotic dose optimisation is required for critically ill patients due to significant alterations in pharmacokinetics (PK).
- Current literature demonstrates clinical outcome benefits associated with antibiotic PK/pharmacodynamics (PD) for most classes of antibiotics including aminoglycosides, beta lactams, fluoroquinolones, linezolid and glycopeptides.
- Minimum inhibitory concentration-linked PK/PD indices have associated limitations that can oversimplify current dose-optimisation approaches and confound clinical outcomes.
- Model-based antibiotic dose optimisation is vital for overcoming limitations of fixed PK/PD indices and will be assisted by new precision medicine technologies to better treat septic and septic shock in critically ill patients.
- Further well designed research is imperative to quantify the level of patient-centred and healthcare-system benefit associated with current and emerging antibiotic dose optimisation approaches including the benefits of therapeutic drug monitoring and model-informed precision dosing.

A HISTORICAL PERSPECTIVE

Since the 1940s, extensive research has been undertaken to describe antibiotic PK/PD [6–8]. The experiments of Dr Harry Eagle and later, Dr William A. Craig, enabled the characterisation of the three PK/PD indices used today: the percentage of time drug concentration remains above the MIC (%$T_{>MIC}$), the ratio of area under the drug concentration-time curve to MIC (AUC_{24}:MIC) and the ratio of drug maximum concentration to MIC (C_{MAX}:MIC) [9,10]. These three indices relate a summary PK measure of antibiotic exposure, normalised to a summary PD parameter of antibiotic potency, usually the minimum inhibitory concentration (MIC) [11]. Using in-vivo (e.g. neutropenic mouse thigh) and in-vitro (e.g. dynamic hollow-fibre) infection models, an assessment of antibiotic efficacy can be made by elucidating a PK/PD target, describing the magnitude of the PK/PD index required to achieve a desired response [12]. These animal studies and in-vitro methods are crucial for preclinical antibiotic drug development and have demonstrated translational validity for human subjects [8,13,14]. However, to extrapolate this data to special patient populations (e.g. critically ill, pregnant, neonatal, burns etc.), ongoing research is required to characterise optimal dosing strategies [9,14,15]. This is particularly relevant for critically ill patients due to their significantly altered PK and incidence of less susceptible pathogens with higher MICs [16,17].

RATIONALE FOR DOSE OPTIMISATION IN CRITICALLY ILL PATIENTS

Profound pathophysiological changes that occur in critically ill patients can significantly affect the PK of antibiotics used [16]. Diagnosed conditions not limited to sepsis, can drive events like third-spacing, organ dysfunction [18–22], vasopressor use, augmented renal clearance (ARC) [23–26], protein losses [27], as well as the use of organ supports including extracorporeal membrane oxygenation (ECMO) and renal replacement therapies (RRT) [28,29▪,30,31▪]. Complex interplays of these changes and organ support treatments can either increase or decrease drug exposure, potentially leading to toxicity or treatment failure respectively [32]. Further, sub-optimal antibiotic exposures can increase chances of the emergence of antimicrobial resistant pathogens from selection pressure and/or adaptive resistance [33–35]. This highlights the imperative of dosing strategies that enhance the probability of achieving optimal drug concentrations, that is, concentrations that (i) maximise the likelihood of clinical success and minimise (ii) the development of resistance to antibiotics and (iii) drug toxicity.

OPTIMAL PHARMACOKINETICS/PHARMACODYNAMICS TARGETS THAT IMPROVE CLINICAL OUTCOMES

Positive clinical outcomes like mortality, clinical cure and microbiological eradication have been associated with achievement of PK/PD targets in at least retrospective cohort studies [32]. A summary of these data are provided below, with a focus on recent data, as well as data of thresholds for related toxicities.

Aminoglycosides

The optimal PK/PD target for aminoglycosides is mostly agreed, even though clinical dosing practice varies internationally [36,37]. C_{MAX}:MIC $\geq$8–10 mg/l has often been used as the index for efficacy, however was designed for multiple daily dosing, with questionable predictive performance in critically ill patients [36,38]. Once daily dosing of tobramycin has shown improved clinical success with achievement of targets AUC_{24}:MIC $\geq$110 mg h/l [39]. Nephrotoxicity and ototoxicity have been associated with amikacin C_{MIN} >5 mg/l or AUC >300 mg h/l [40–42]. For gentamicin and tobramycin, a C_{MIN} >1 mg/l has also been associated with the same toxicities [43–47].

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Aminoglycoside TDM has been associated with increased efficacy, reduced hospital length of stay and reduced toxicity in hospitalised patients [48].

Beta-Lactams

Beta-lactams demonstrate time-dependent bacterial killing, indicating the optimal PK/PD index as the percentage of time free drug concentration remains above the MIC [7]. Preclinical studies suggest that maintenance of 40–70% $fT_{>4 \times MIC}$ allows for maximum bactericidal effect [49]. Other evidence advocates for maintaining 100% $fT_{>1 \times MIC}$ as a surrogate target for 40–70% $T_{>4 \times MIC}$ [50]. The DALI study revealed that achieving 100% $fT_{>1 \times MIC}$ led to superior clinical outcomes compared to lower concentrations [32], and there is some evidence to suggest aiming for higher PK/PD targets, for instance 100% $fT_{>4–5 \times MIC}$ also improves outcomes including clinical cure, microbiological eradication and emergence of resistance for critically ill patients [51–53]. These PK/PD indices are higher than have been established in preclinical infection models which can range from 20 to 70% $fT_{>1 \times MIC}$. Infusion durations have also been shown to play an important role in achieving target antibiotic concentrations as well as outcomes. A recent systematic review and meta-analysis has shown that prolonged infusion of beta-lactams can significantly reduce all-cause mortality and enhance outcomes when compared to intermittent infusions in patients with sepsis [54]. BLING-III, a large multisite RCT will further assess the effect of continuous vs. intermittent beta-lactam infusions on outcomes for critically ill patients. Its PK/PD sub-study is expected to better elucidate PK/PD targets and is due to be published soon [55].

The benefits of TDM for have been somewhat more difficult to define. A recent systematic review and meta-analysis of TDM for beta-lactams has shown a statistically significant improvement in clinical and microbiological cure, as well as reduction in treatment failure [56▪▪]. Although this study did not include the DOLPHIN trial, an RCT to assess the benefit of model-informed precision dosing (MIPD) vs. standard dosing of piperacillin/tazobactam on length of stay in ICU patients [57▪▪]. The DOLPHIN trial failed to find any meaningful differences between groups, although may have been compromised by significant limitations, most importantly, an inability for the intervention to increase achievement of target antibiotic concentrations [58]. Further, the TARGET trial, a multicentre German RCT to assess the benefit of TDM-guided vs. fixed-dose continuous infusion of piperacillin/tazobactam was unable to show improved SOFA scores (primary outcome) amongst patients with sepsis. The trial demonstrated numerically lower 28-day mortality rates, improved clinical cure and microbiological eradication, though these outcomes did not reach statistical significance. Notably, there was a significant improvement in achievement of target antibiotic concentrations in the TDM group, despite rates remaining disappointingly low (37% vs. 15%), although these low proportions may relate to the narrow target concentration range selected [59▪▪].

Daptomycin

AUC_{24}:MIC is the PK/PD index most correlated with efficacy for daptomycin, although heterogeneity exists in potential targets [60]. An AUC_{24}:MIC > 666 mg h/l was described to be the optimal target for treatment of *S. aureus* [61], with free drug $fAUC_{24}$:MIC >27.4 mg h/l described as the optimal target for treatment of enterococcal blood stream infections [62]. The most relevant toxicity is creatine phosphokinase elevation has increased an probability of occurrence where C_{MIN} >19.5 mg/l and C_{MIN} >24.3 mg/l as found in two studies [63,64]. The benefits of TDM have been difficult to define as there are currently no published studies that compare the effect of TDM-guided vs. fixed dosing on outcomes [60].

Fluoroquinolones

For ciprofloxacin, a PK/PD exposure of AUC_{24}:MIC ≥125 mg h/l was shown to be associated with clinical and microbiological cure [65]. Another study of Gram-negative bacteraemia showed a AUC_{24}:MIC ≥250 mg h/l as significant for improving rates of clinical cure [66]. Fluoroquinolone-associated seizures have been reported in literature however no toxicity threshold has been defined and causality is confounded by other seizure-related risk factors [67–69]. The benefit of MIPD vs. standard dosing of ciprofloxacin on ICU length of stay was also explored in the DOLPHIN trial, however outcomes were similar to the piperacillin/tazobactam arm, with a failure of the intervention to increase achievement of target antibiotic concentrations [57▪▪].

Linezolid

Clinical cure and bacteriological eradication have been demonstrated at targets of 82–99% $fT_{>MIC}$ as well as AUC_{24}:MIC = 80–120 mg h/l [6]. AUC_{24}:MIC >100 mg h/l have been suggested to improve outcomes in critically ill patients, with increased probability of achieving target antibiotic concentrations

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by using continuous infusion vs. intermittent dosing [70,71]. Thrombocytopenia, a problematic side effect associated with linezolid treatment, has been reported to occur at C_{MIN} of >7 mg/l or AUC_{24} of >300 mg h/l. TDM has been demonstrated to reduce risk of thrombocytopenia toxicity whilst retaining efficacy [72–74].

Vancomycin

Studies of at least retrospective cohort design have shown positive mortality and survival benefits in relation to AUC_{24}:MIC targets for vancomycin. Most notably for the treatment of *S. aureus* bacteraemia, a target AUC_{24}:MIC of >373 mg h/l has been associated with a significant reduction in all-cause mortality [75]. Improved survival has also been demonstrated in patients with septic shock from MRSA bacteraemia, with two significant AUC_{24}:MIC thresholds for survival, ≥451 mg h/l and ≥578 mg h/l [76]. It is important to note that many outcome studies demonstrate a wide range of AUC_{24}:MIC thresholds (values ranging from 211to 667 mg h/l) [77]. Consensus recommendations have suggested AUC_{24}:MIC 400–600 mg h/l as the target appropriate for effective clinical outcomes [78,79], however a recent systematic meta-analysis has suggested the predictive performance of AUC_{24}:MIC for clinical outcomes to be modest and inconsistent [77]. Several studies continue to demonstrate the value of TDM for vancomycin, most notably monitoring of AUC as opposed to trough concentrations in order to significantly reduce rates of nephrotoxicity whilst maintaining treatment efficacy [80–85].

CURRENT LIMITATIONS IN APPROACHES TO DOSE OPTIMISATION

Whilst PK/PD indices have been cornerstone metrics in antibiotic development and current methods of dose optimisation, they still have limitations that effect their predictive performance in clinical practice.

Minimum inhibitory concentration considerations

MIC is a static pharmacodynamic measure designed to assess antibiotic susceptibility under laboratory conditions and does not accurately represent the complex and dynamic in vivo environment where bacterial concentrations may be different and antibiotic exposure is constantly changing, particularly in the context of infections in different physiological compartments [86,87]. Significant variability can exist within and between laboratories, as well as between assays (e.g. broth microdilution vs. E-test) and has been suggested to be a substantial limiting factor to accurate MIC determination, with an error magnitude of at least twofold [88]. These inaccuracies are propagated into the PK/PD index, potentially misinforming dosing selection and the ability to achieve target antibiotic concentrations [89▪]. Clinically, the growth time required for MIC determination can delay results (up to 72 h) and further impede appropriate antibiotic selection and dosing adjustments [90]. Practically speaking, MIC results must be conceptualised as fluctuating value with consideration given to wild-type distributions and epidemiological cut-off scores, opposing the idea that a fixed-value "true" MIC exists [87,90,91].

Static nature of indices

PK/PD indices rely on a single time-point measurement (usually at 24 h) to assess the impact of antibiotic treatment on the entire bacterial population, ignoring the complex dynamic changes in bacterial behaviour in response to treatment, and whether bacterial populations are increasing, decreasing, or developing resistance over time [89▪]. The optimal PK/PD index and its predictive performance can change depending on the patient population, outcome assessed, time of determination and infection site/target or tissue (e.g. plasma vs. interstitial fluid) [92]. For example the most predictive PK/PD index for cefuroxime efficacy will fluctuate between % $T_{>MIC}$ and AUC_{24}:MIC depending on different conditions, including the magnitude of MIC [93]. Further unaccounted for within the indices are the effects of the host response (e.g. immune system and effect of neutrophils), inoculum size, persistent bacteria, interactions between different antibiotics (and other prescribed medicines) as well as their combined effects (synergy or antagonism) [89▪,94].

Plasma vs. site-of-infection concentrations

Antibiotic concentrations taken from plasma samples may not accurately reflect concentrations at the infection site, potentially leading to suboptimal therapy. This is due to variations in tissue penetration, local metabolism, as well as physiochemical properties of the antibiotic [95]. Fundamentally, clinician expertise is still required to interpret and extrapolate plasma antibiotic concentrations and the effects in different physiological compartments.

Dose adaptation

Many studies often include a cap on maximum doses to avoid drug toxicity. While this may be considered a safety measure, it can severely constrain the ability

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to achieve or improve target antibiotic concentrations. This is particularly important to consider in clinical outcome studies of TDM and MIPD for critically ill patents, where results may not accurately reflect the benefit of higher, yet safe, drug concentrations.

Future strategies

Strategies for improving antibiotic dosing in critically ill should reflect effective, integrated and multifaceted technological approaches. This could involve leveraging artificial intelligence, machine learning, advanced PK/PD modelling as well as micro-sampling and genomics to allow for the delivery of more effective, personalised and adaptative approaches to treat sepsis and septic shock, and prevent the emergence of resistance (Fig. 1). It is important to highlight however, that the feasibility of these technologies is a great challenge given global disparity in access to tools and expertise required for implementation. Developed countries are slowly pioneering the research and integration of these complex methods into clinical practice, while some countries may continue to use product information for dosing, highlighting economic, infrastructural and expertise gaps. The ability to bridge this divide will demand expert international collaboration, knowledge sharing and the creation of adaptable solutions across diverse healthcare systems to ensure that innovations in antibiotic dose optimisation can be of benefit to all patients, irrespective of their location.

Advanced and integrated pharmacokinetics/pharmacodynamics modelling

Advanced modelling techniques including population PK (PopPK), physiological-based PK (PBPK), as well as mechanism-based models of dynamic preclinical models are powerful tools that may be combined together to redefine PK/PD indices [9,11,92,96]. These methods may better describe the time-course of antibiotic exposure and bacterial response, with the ability to model increasingly complex processes including organ function, tissue distribution, immune-system function, inoculum effect, role of biomarkers, as well as important resistance mechanisms [96,97–99]. Already, the use of PopPK models in conjunction with Monte Carlo

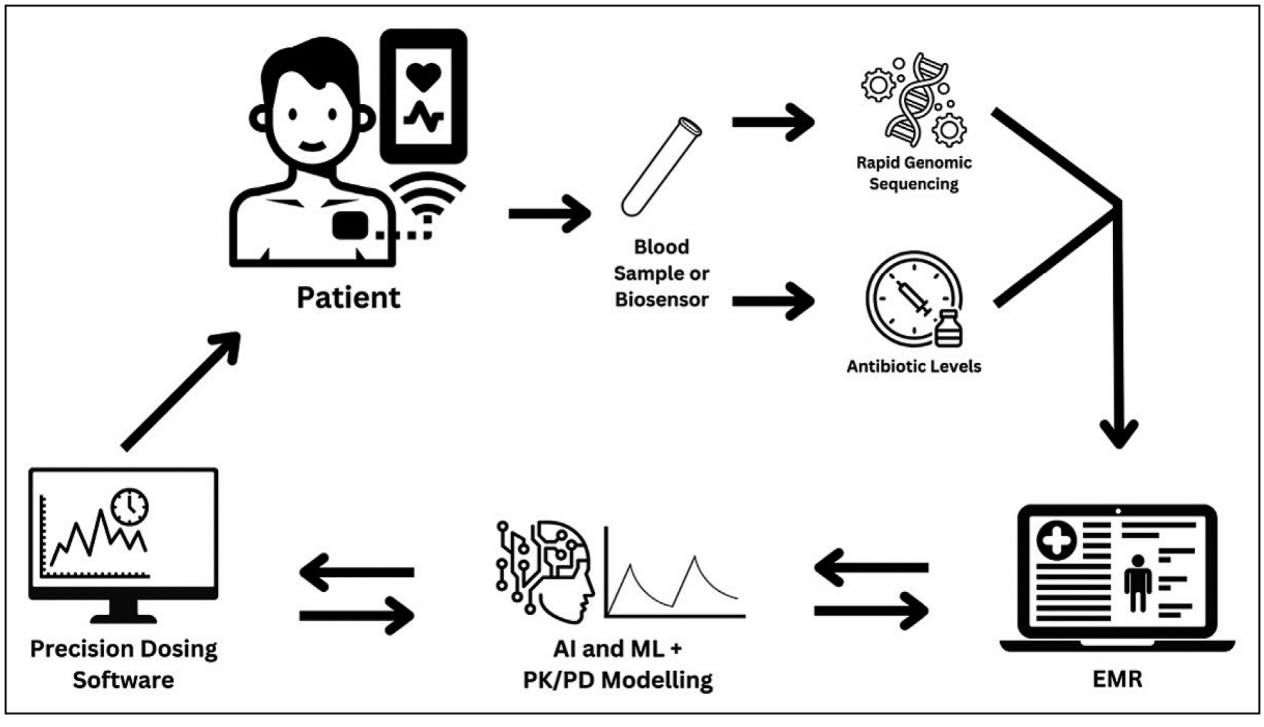

FIGURE 1. Future approaches to antibiotic dose optimisation in the ICU. Schematic illustration of novel technology integration for antibiotic dose optimisation. Patient wears biosensor, or usual blood draw feeds genomic testing to allow for early pathogen detection and appropriate antibiotic selection. Patient electronic medication record merges biosensor and lab data with artificial intelligence, machine learning and PK/PD modelling to analyse data and predict optimal antibiotic exposure. Precision dosing software assists selection of optimised dose to be administered to patient. Continuous and adaptive feedback proceeds allowing for iterative development of underlying pharmacokinetic models to improve dosing precision.

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simulations and Bayesian forecasting have been utilised extensively to characterise the time-course of antibiotic exposures in specific patient groups like the critically ill. Integration with dosing software has enabled the development and clinical application of MIPD for individual patients [100,101,102▪], with growing evidence to support its use [103▪▪]. The addition of mechanism-based modelling may further inform MIPD approaches, however, requires further research for bedside translation [104].

Rapid and personalised precision medicine

The use of rapid metagenomics to identify pathogen susceptibility, resistance and virulence, can enable early and accurate antibiotic selection to prevent prolonged therapy and minimise broad-spectrum antibiotic use [105–109]. Wearable gadgets that use novel micro-sampling techniques, offer the capability to track patient response to antibiotic therapy, gathering vital data on patient characteristics, drug concentrations, signs of infection, and organ function. Utilising this data, antibiotic dosing can be adapted in real time through model-informed feedback to continuously optimise therapy [110–113]. Further integration with artificial intelligence and machine learning could allow for continuous learning capability that can merge with electronic medical records to automate and complement pharmacometrics for iterative PK/PD model development as well as clinical decision and MIPD support [114▪,115,116]. More recently, hybrid machine learning techniques have been shown to predict antibiotic concentrations with high accuracy [117].

Research design and output

Despite the large amount of research on antibiotic dose optimisation and its effect on patient outcomes, the clinical impact of these studies has been limited by several factors. These include small sample sizes, insufficient statistical power, and sub-optimal study design, all of which can constrain the ability to observe statistically significant outcomes [58,118,119]. A recent systematic review has highlighted these concerns in methodological validity, and suggests a unified standard for study design and reporting to maintain research interpretability, relevance and translational validity [119]. It follows that there is a requirement for larger RCTs that are focused on detecting differences at key time-points for well defined patient-centred outcomes like mortality, clinical cure, duration of organ support, or length of stay in the population of interest. Subsequently, the health-economic benefits also need to be investigated, as well as the barriers to further research and viability of implementation [120].

CONCLUSION

There is an imperative to continue to explore scientifically robust approaches for describing correlations between antibiotic exposure to microbiological and clinical effects. It is clear there is an relationship with improvement in patient-centred clinical outcomes with use of PK/PD techniques with TDM and MIPD proving useful for special populations like the critically ill. Well designed trials need to be conducted to quantify the level of benefit, and to further explore the role of integrated PK/PD modelling and advanced technologies in taking steps towards personalised and precision dosing approaches to improve outcomes when treating sepsis and septic shock in these patients.

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Conflicts of interest

There are no conflicts of interest.

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